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EFFECTS OF PASSIVE SMOKING IN THE MULTIPLE RISK FACTOR INTERVENTION TRIAL

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The Multiple Risk Factor Intervention Trial (MRFIT), conducted in 1973–1982, provided a unique opportunity to study the effect of passive smoking on men whose wives smoke. MRFIT participants who reported at entry that they had never smoked tobacco products were classified according to the smoking status of their wives. Men with wives who smoked had similar mean levels of serum thiocyanate (54.3 vs. 53.9 μmol/liter, $p = 0.83$) but higher mean levels of expired carbon monoxide (7.7 vs. 7.1 ppm, $p = 0.001$). Lower levels of pulmonary function (by maximum forced expiratory volume in one second) were also observed in these men (3,493.1 vs. 3,591.9 ml, $p = 0.04$). The relative risks, for men whose wives smoked compared with men whose wives did not smoke, for the endpoints coronary heart disease death, fatal or nonfatal coronary heart disease event, and death from any cause were 2.11 ($p = 0.19$, 95% confidence interval (CI) 0.69–6.46), 1.48 ($p = 0.13$, 95% CI 0.89–2.47), and 1.96 ($p = 0.08$, 95% CI 0.93–4.11), respectively. When smokers who quit prior to entry were included in the analyses, the relative risks, for men whose wives smoked compared with men whose wives did not smoke, for the above endopoints were 1.45 ($p = 0.25$, 95% CI 0.77–2.73), 1.19 ($p = 0.29$, 95% CI 0.85–1.65), and 1.72 ($p = 0.01$, 95% CI 1.12–2.64), respectively. These relative risk estimates did not change appreciably after adjusting for other baseline risk factors. The results suggest that passive exposure to cigarette smoke may have a deleterious impact on the health of nonsmokers and that nonsmokers may be at an increased risk of death through passive exposure to cigarette smoke.

coronary disease; tobacco smoke pollution

Passive smoking is defined as exposure of an individual to the air pollution resulting from another person's tobacco smoke. The products of tobacco smoke are divided

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Abbreviations: FEV_1, forced expiratory volume in one second; MRFIT, Multiple Risk Factor Intervention Trial.

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into two components. Those directly exhaled by the smoker are called mainstream smoke, while those from the lit end of the cigarette, cigar, or pipe which are discharged into the environment are referred to as sidestream smoke. The composition of sidestream smoke (1) differs substantially from that of mainstream smoke, depending upon the different temperatures at which the substances burn and the available oxygen supply. Particulates, for example, are about 10 times greater in mainstream smoke than in sidestream smoke. After inhalation, sidestream smoke probably reaches the more distant alveolar spaces in the lung (2). Sidestream smoke also contains much more free nicotine in the gas phase, generates more carbon monoxide (1), and contains much higher concentrations of the reduced products of nitrogen including several highly carcinogenic substances (3). Most environmental tobacco smoke is from sidestream smoke, and only a very small amount is from exhaled mainstream smoke. Environmental exposures to tobacco smoke depend on the number of smokers in the area and the amount they smoke, the size of the area, and the ventilation rate.

It is now an accepted fact that cigarette smokers have an increased risk of many diseases. In recent years, there has been a growing concern that nonsmokers exposed to environmental tobacco smoke may also be at increased risk of certain diseases, especially cancer, chronic obstructive pulmonary disease, and, possibly, heart disease.

Friedman et al. (4) reported that 63.3 per cent of adults were exposed to passive smoking for at least one hour per week. A higher percentage was exposed away from home, usually at work. Repace and Lowrey (5) have estimated that the exposure to environmental tobacco smoke of the nonsmoking adult population was about 1.43 mg of tar per day. A cigarette smoker, on the other hand, can be expected to inhale about 420 mg of tar per day (14 mg of tar per cigarette for an average of 30 cigarettes per day). Thus, the dose from passive smoking is much less than the dose from cigarette smoking.

Studies on passive smoking reported to date have depended on self-reported histories of environmental tobacco smoke exposure. A workshop on the respiratory effects of environmental tobacco smoke in 1983 sponsored by the Division of Lung Diseases at the National Heart, Lung, and Blood Institute (6) noted that lack of objective measures of dose or exposure, confounding variables, methods of statistical analysis, and quantification of other variables were major concerns in the evaluation of current and future studies.

Participants in the Multiple Risk Factor Intervention Trial (MRFIT) (7) offered an unusual opportunity to study the effect of environmental tobacco smoke on men, especially in the home. Objective measures of cigarette smoking behavior, as well as other critical risk factors for cardiovascular and other diseases, were carefully monitored in a large population followed for an average of seven years. Fortuitously, at entry into the study, prior to randomization, a detailed smoking history was obtained for each of the participants subsequently randomized. This history included not only their own smoking history but also that of their wives, family members, and coworkers. This trial, to our knowledge, is the first longitudinal study that was able to objectively define the participants' smoking status and possible exposure to environmental tobacco smoke. The study design was also unique because the index subjects were men who did not smoke and who were at high risk of heart disease, and the exposure in-

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dex was the smoking behavior of their wives.

MATERIALS AND METHODS

The Multiple Risk Factor Intervention Trial was a primary prevention trial designed to test the effect of a multifactor intervention program on mortality from coronary heart disease.

The design of the MRFIT has been described (7). Briefly, men aged 35–57 years were recruited in 18 US cities. They were screened to select those in the upper 10–15 per cent of a risk score distribution derived from Framingham data, based on serum cholesterol concentration, cigarette smoking, and diastolic blood pressure. Those free of overt coronary heart disease by history and resting electrocardiogram who consented to participate were randomized to either the special intervention or usual care groups. After randomization, special intervention men participated in an intensive intervention program aimed at lowering blood cholesterol by nutritional means, eliminating cigarette smoking through education and behavior modification techniques, and reducing the diastolic blood pressure of those who were hypertensive primarily by using a stepped-care drug regimen. Usual care participants were referred to their customary source of medical care with information on their risk factor status but with no advice as to intervention. Both special intervention and usual care participants were seen annually over six to eight years for risk factor measurement and a medical examination. A detailed smoking history was obtained from all participants during screening and at each annual visit.

This paper focuses on the effects of passive smoking on participants who reported that they did not smoke cigarettes, pipes, cigars, or cigarillos prior to randomization into the trial. Most analyses are restricted to men who had never smoked cigarettes. Endpoint results are shown for never smokers and all nonsmokers at entry; nonsmokers included never smokers and exsmokers who quit prior to entry into the study. Data on the smoking habits of the participants' wives were collected at baseline for participants who smoked and those who did not smoke. The smoking status of the wife is used as an index of passive smoking exposure for the men who did not smoke. Only a limited amount of information was collected about exposure to tobacco smoke on the job. Participants were asked the smoking status of their coworkers. The results of all analyses presented are for the special intervention and usual care groups combined. Separate analyses for each study group yielded similar results.

Measurements of smoking exposure

Serum thiocyanate was measured during screening and at each annual visit. In the planning stages of the MRFIT, it was recognized that special intervention participants who were repeatedly urged to stop or reduce smoking cigarettes might be more likely to misreport their cigarette smoking status than usual care participants. Serum thiocyanate is elevated in smokers because of the cyanide present in tobacco smoke which is metabolized to thiocyanate. The half-life of serum thiocyanate is approximately 14 days, reflecting long-term exposure to cigarette smoke.

At the third and sixth annual examinations, expired air carbon monoxide was measured, using an ecolyzer (series 2000, Energetics Science, Inc., Elmsford, NY), which permitted a visual meter reading on a 0–100 parts per million (ppm) scale. The levels of expired air carbon monoxide are directly related to carboxyhemoglobin in the blood. The half-life of elevated carboxyhemoglobin levels after exposure to environmental carbon monoxide is only two to four hours; thus, its measurement reflects only very recent exposures. Other factors, especially any incomplete combustion of carbon-containing substances, can increase environmental carbon monoxide levels and blood carboxyhemoglobin levels.

Pulmonary function testing was conducted at screening and at each annual examination using a 10-L Stead Wells

water-filled spirometer (Warren E. Collins, Inc., Braintree, MA). The forced expiratory volume in one second (FEV_1) is defined as the volume of gas exhaled over an interval of one second, with expiration as rapid and as complete as possible. The selection of tracings for analysis was based on careful quality control standards defined prior to the current analyses. The maximum of three to five measurements meeting quality standards (maximum FEV_1), adjusted for age and height, is used to quantify pulmonary function in this paper. The quality control procedures and measurement techniques are described in detail elsewhere (8).

Endpoints

Classification of cause of death was performed by a committee of three cardiologists who were unaware of treatment assignment (special intervention/usual care) or passive smoking status. They used hospital records, physicians' reports, next-of-kin interviews, death certificates, and autopsy reports, when available. Coronary heart disease deaths were subclassified as 1) documented myocardial infarction; 2) sudden death within 60 minutes, or between one and 24 hours of symptom onset, without documented myocardial infarction; 3) congestive heart failure due to coronary heart disease; or 4) death associated with surgery for coronary heart disease. Results are also presented for the endpoint fatal or nonfatal coronary heart disease event. This endpoint includes coronary heart disease death, serial change from baseline on a resting electrocardiogram, and/or documented evidence of myocardial infarction from a review of hospital records by a panel of physicians (9).

Statistical methods

Differences in baseline characteristics and changes in risk factor levels from baseline to the sixth annual examination for men who did not smoke who had wives who smoked versus men who did not smoke who had wives who were also nonsmokers were tested for statistical significance using the Student's t test (two-sided) or the 2×2 chi-square test. For comparison of measures of smoking exposure between the two groups, mean levels of thiocyanate and the maximum FEV_1 were calculated for baseline and the average of baseline and all follow-up visits. The latter results in improved precision but smaller sample size. The maximum FEV_1 means were adjusted for age and height by analysis of covariance. Mean levels of expired air carbon monoxide were calculated for year 3 and the average of years 3 and 6. Differences in the means between the two groups for thiocyanate and expired air carbon monoxide were assessed by the Student's t test. Differences in the adjusted means for maximum FEV_1 were assessed by analysis of covariance. Tests for a dose effect of smoking exposure were performed using regression models with number of cigarettes smoked per day reported by wife as an independent variable.

Relative risk estimates, for men whose wives smoked compared with men whose wives did not smoke, for the endpoints death from any cause, coronary heart disease death, and fatal or nonfatal coronary heart disease event were calculated using the Cox proportional hazards model (10) with Breslow's approximation (11). Results are shown both unadjusted and adjusted for age, baseline blood pressure, cholesterol, weight, education (as a measure of socioeconomic status), and drinks per week.

RESULTS

Sample size

There were 1,400 of 12,866 randomized participants who reported that they had never smoked cigarettes, pipes, cigars, or cigarillos at entry into the MRFIT. Of these never smokers, 1,245 were married; 286 to women who smoked and 959 to women who did not smoke (table 1).

Comparability of never smokers by smoking status of wife

Baseline characteristics of these 1,245 men by smoking status of wife are sum-

marized in table 2. The two groups of men are similar with respect to age, blood pressure, and cholesterol. The average weight for men with wives who smoked was 4.2 pounds greater than that of men whose wives did not smoke ($p < 0.01$). Men whose wives smoked consumed an average of 2.1 more alcoholic drinks per week ($p < 0.01$) and had 0.5 years less formal education than men with wives who did not smoke ($p < 0.05$). Income was similar between the groups. Table 3 shows risk factor changes and the percentage of men prescribed antihypertensive medications at the sixth annual examination by smoking status of wife. There were no statistically significant differences between the two groups.

TABLE 1

Frequency distribution of smoking status at entry: Multiple Risk Factor Intervention Trial, 1973–1982

	n	%
Smokers*	9,244	71.8
Ex-smokers	2,222	17.3
Never smokers	1,400	10.9
Not married	155	1.2
Wife a nonsmoker	959	7.5
Wife a smoker	286	2.2
Total	12,866	100.0

* Includes smokers of cigarettes, pipes, cigars, or cigarillos.

Comparisons of smoking exposure

Mean serum thiocyanate levels at baseline and the average of baseline and all annual follow-up visits are shown in table

TABLE 2

Mean values of selected variables at entry for 1,245 men who reported never smoking cigarettes, pipes, cigars, or cigarillos, by smoking status of wife at entry: Multiple Risk Factor Intervention Trial, 1973–1982

	Smoking status of wife		Difference*	95% confidence interval
	Smoker (n = 286)	Nonsmoker (n = 959)		
Age (years)	47.4	47.5	−0.2	−1.0–0.6
Diastolic blood pressure (mmHg)	103.3	103.1	0.2	−0.4–0.9
Systolic blood pressure (mmHg)	152.3	150.8	1.5	−0.4–3.4
Serum cholesterol (mg/dl)	266.0	264.4	1.6	−2.3–5.5
High density lipoprotein cholesterol (mg/dl)	43.4	42.7	0.7	−0.7–2.0
Low density lipoprotein cholesterol (mg/dl)	166.5	167.1	−0.6	−5.0–3.9
Weight (lbs)	194.6	190.4	4.2	0.6–7.8
Drinks/week (n)	9.7	7.6	2.1	0.8–3.3
Education (years)	13.8	14.2	−0.5	−0.9–0.0
Income (1,000$)	22.1	22.3	−0.1	−1.4–1.2

* Difference may not agree because of rounding.

TABLE 3

Mean change in selected variables (sixth annual minus baseline examination) for men who reported never smoking cigarettes, pipes, cigars, or cigarillos, by smoking status of wife at entry: Multiple Risk Factor Intervention Trial, 1973–1982

	Smoking status of wife		Difference	95% confidence interval
	Smoker (n = 266)	Nonsmoker (n = 889)		
Diastolic blood pressure (mmHg)	−10.1	−9.9	−0.3	−1.7–1.1
Systolic blood pressure (mmHg)	−12.6	−13.6	1.1	−1.1–3.2
Plasma cholesterol (mg/dl)	−11.4	−11.0	−0.4	−4.7–3.9
High density lipoprotein cholesterol (mg/dl)	−1.4	−0.7	−0.7	−1.9–0.5
Low density lipoprotein cholesterol (mg/dl)	−10.8	−10.4	−0.4	−4.4–3.7
Weight (lbs)	−2.2	−2.5	0.3	−1.4–2.0
Drinks/week (n)	−2.7	−2.1	−0.6	−1.7–0.4
On antihypertensive medication (%)	66.5	62.5	4.0	−2.7–10.6

4 by smoking status of wife. The mean thiocyanate levels are similar for the two groups, both at baseline and averaged over all visits.

Expired air carbon monoxide was measured at the third and sixth annual examinations. The average expired air carbon monoxide at the third annual examination for men whose wives smoked was 7.7 ppm compared with 7.1 ppm for men whose wives did not smoke (table 5). The difference, 0.6, is statistically significant ($p = 0.001$), as is the test for linear trend ($p = 0.03$). Similar results were obtained when the averages of the third and sixth annual carbon monoxide measurements were combined.

Men with wives who smoked had significantly lower levels of pulmonary function at baseline as measured by the maximum FEV_1 (table 6). The mean maximum FEV_1 is 3,493.1 ml for men whose wives smoked versus 3,591.9 for men whose wives did not smoke, a difference of about 100 ml. Similar results were obtained when averaging over all visits, although the difference between the two groups was not statistically significant ($p = 0.16$).

Endpoint results for never smokers

Table 7 gives the event rates by smoking status of wife and table 8 shows the relative risk estimates (for men who did not smoke whose wives smoked compared with those whose wives did not smoke) for the endpoints death from any cause, coronary heart disease death, and fatal or nonfatal coronary heart disease event.

TABLE 4

Mean levels of thiocyanate (μmol/liter) at baseline and average over all visits for men who reported never smoking cigarettes, pipes, cigars, or cigarillos, by smoking status of wife at entry: Multiple Risk Factor Intervention Trial, 1973–1982

Smoking status of wife	Baseline		Average over all visits	
	n	Mean	n	Mean
Nonsmoker	878	53.9	704	51.6
Smoker	264	54.3	212	52.3
1–19 cigarettes/day	125	54.0	102	51.6
≥20 cigarettes/day	139	54.6	110	52.9
Smoker/nonsmoker difference	0.4 (−3.7, 4.6)*		0.7 (−2.7, 4.0)	
p value for linear trend	0.99		0.55	

* 95% confidence limits.

TABLE 5

Mean expired air carbon monoxide (ppm) at the third annual visit and average over all visits for men who reported never smoking cigarettes, pipes, cigars, or cigarillos, by smoking status of wife at entry: Multiple Risk Factor Intervention Trial, 1973–1982

Smoking status of wife	Third annual visit		Average over all visits	
	n	Mean	n	Mean
Nonsmoker	828	7.1	780	6.7
Smoker	244	7.7	228	7.1
1–19 cigarettes/day	112	7.7	106	7.1
≥20 cigarettes/day	132	7.8	122	7.2
Smoker/nonsmoker difference	0.6 (0.2, 1.0)*		0.5 (0.2, 0.7)	
p value for linear trend	0.03		<0.01	

* 95% confidence limits.

TABLE 6

Mean maximum FEV_1 (ml) adjusted for age and height at baseline and average over all visits for men who reported never smoking cigarettes, pipes, cigars, or cigarillos, by smoking status of wife at entry: Multiple Risk Factor Intervention Trial, 1973–1982

Smoking status of wife	Baseline		Average over all visits	
	n	Mean	*n*	Mean
Nonsmoker	514	3,591.9	257	3,491.3
Smoker	162	3,493.1	81	3,403.3
1–19 cigarettes/day	66	3,412.1	31	3,263.3
≥20 cigarettes/day	96	3,548.8	50	3,489.0
Smoker/nonsmoker difference	−98.9 (−192.4, −5.4)*		−87.8 (−210.7, 35.2)	
p value for linear trend	0.52		0.99	

* 95% confidence limits.

TABLE 7

Number of deaths from any cause and from coronary heart disease and fatal or nonfatal coronary heart disease events for men who reported never smoking cigarettes, pipes, cigars, or cigarillos, by smoking status of wife at entry: Multiple Risk Factor Intervention Trial, 1973–1982

Smoking status of wife	No. of men	Death from any cause	Coronary heart disease death	Fatal or nonfatal coronary heart disease event
Nonsmoker	959	19 (2.83)*	8 (1.19)	48 (7.28)
Smoker	286	11 (5.55)	5 (2.52)	21 (10.81)
1–19 cigarettes/day	133	3 (3.21)	1 (1.07)	8 (8.70)
≥20 cigarettes/day	153	8 (7.65)	4 (3.82)	13 (12.71)
p value for linear trend†		0.08	0.04	0.20

* Rates per 1,000 person-years.

† From Cox proportional hazards regression using number of cigarettes smoked per day by wife as a covariate.

TABLE 8

Relative risk estimates, wife who smoked compared with wife who did not smoke, and their 95 per cent confidence intervals for men who reported never smoking cigarettes, pipes, cigars, or cigarillos: Multiple Risk Factor Intervention Trial, 1973–1982

Endpoint	Relative risk	*p* value	95% confidence interval
Death from any cause			
Unadjusted	1.96	0.08	0.93–4.11
Adjusted*	1.94	0.08	0.91–4.09
Coronary heart disease death			
Unadjusted	2.11	0.19	0.69–6.46
Adjusted	2.23	0.17	0.72–6.92
Fatal or nonfatal coronary heart disease event			
Unadjusted	1.48	0.13	0.89–2.47
Adjusted	1.61	0.07	0.96–2.71

* Adjusted by Cox proportional hazards regression for age, baseline blood pressure, cholesterol, weight, drinks per week, and education.

As of February 28, 1982, after an average of seven years of follow-up, 11 of 286 men married to smokers had died (5.6 per 1,000 person-years) compared with 19 of 959 men married to nonsmokers (2.8 per 1,000 person-years). There is some suggestion of a dose effect for the endpoint death from any cause, with 3.2 deaths per 1,000 person-

years in the category wife smokes 1–19 cigarettes per day and 7.7 deaths per 1,000 person-years in the category wife smokes 20 or more cigarettes per day, although the test for a linear trend was not significant ($p = 0.08$).

The numbers are small for the endpoint coronary heart disease death, but they follow the same pattern as those for the endpoint death from any cause. The coronary heart disease death rate is 2.5 per 1,000 person-years for those whose wives smoked compared with 1.2 for those whose wives did not smoke. The test for a linear trend was significant ($p = 0.04$).

Among men with wives who smoked, there were 10.8 fatal or nonfatal coronary heart disease event endpoints per 1,000 person-years versus 7.3 per 1,000 person-years for those whose wives did not smoke. The event rate is higher for those whose wives smoked 20 or more cigarettes per day compared with those whose wives smoked 1–19 cigarettes per day, although the test for linear trend for the endpoint fatal or nonfatal coronary heart disease was not significant.

The relative risk estimates, for men whose wives smoked compared with men whose wives did not smoke, for the endpoints death from any cause, coronary heart disease death, and fatal or nonfatal coronary heart disease event are 1.96 ($p = 0.08$, 95 per cent confidence interval (CI) 0.93–4.11), 2.11 ($p = 0.19$, 95 per cent CI 0.69–6.46), and 1.48 ($p = 0.13$, 95 per cent CI 0.89–2.47), respectively. These relative risks did not change appreciably after adjusting for other baseline risk factors.

Endpoint results for all nonsmokers

Table 9 presents unadjusted and adjusted relative risk estimates, for men whose wives smoked compared with men whose wives did not smoke, for the endpoints death from any cause, coronary heart disease death, and fatal or nonfatal coronary heart disease event for all nonsmokers at entry; nonsmokers included never smokers and ex-smokers who quit prior to entry into the study. For the endpoint death from any cause, the relative risk estimate is 1.72, which differs significantly from 1.0 ($p = 0.01$, 95 per cent CI 1.12–2.64). For the endpoints coronary heart disease death and fatal or nonfatal coronary heart disease event, the relative risk estimates are 1.45 ($p = 0.25$, 95 per cent CI 0.77–2.73) and 1.19 ($p = 0.29$, 95 per cent CI 0.85–1.65), respectively. As with the analysis restricted to never smokers, adjusting for baseline risk factors did not change the relative risk estimates.

Endpoint results by smoking exposure on the job

Only a limited amount of information was collected about exposure to tobacco

TABLE 9

Relative risk estimates, wife who smoked compared with wife who did not smoke, and their 95 per cent confidence intervals for nonsmokers: Multiple Risk Factor Intervention Trial, 1973–1982*

Endpoint	Relative risk	p value	95% confidence interval
Death from any cause			
Unadjusted	1.72	0.01	1.12–2.64
Adjusted†	1.79	<0.01	1.17–2.76
Coronary heart disease death			
Unadjusted	1.45	0.25	0.77–2.73
Adjusted	1.59	0.15	0.84–3.02
Fatal or nonfatal coronary heart disease event			
Unadjusted	1.19	0.29	0.85–1.65
Adjusted	1.32	0.10	0.95–1.84

* Includes both never smokers and ex-smokers who quit prior to entry into the trial.

† Adjusted by Cox proportional hazards regression for age, baseline blood pressure, cholesterol, weight, drinks per week, education, and past smoking history.

smoke on the job. The participants were asked the smoking status of most of their coworkers. Of 1,237 never smokers, 906 (73.2 per cent) reported that most coworkers were smokers, and 331 (26.8 per cent) reported that most coworkers were nonsmokers. The relative risk for the endpoint death from any cause, for men whose coworkers smoked compared with men whose coworkers did not smoke, adjusted for age and wife's smoking status is 1.2 ($p = 0.63$, 95 per cent CI 0.5–1.8). For the endpoint coronary heart disease death, the relative risk is 2.6 ($p = 0.23$, CI 0.5–12.7), and for fatal or nonfatal coronary heart disease event, the relative risk is 1.4 ($p = 0.26$, CI 0.8–2.5).

Because of the small number of deaths, the joint impact of a spouse who smoked and coworkers who smoked was estimated only for the endpoint fatal or nonfatal coronary heart disease event. The risks for the categories wife and coworkers who smoked, wife who smoked and coworkers who did not smoke, and coworkers who smoked and wife who did not smoke relative to the category wife and coworkers who did not smoke are 1.7 ($p = 0.14$, 95 per cent CI 0.8–3.6), 1.2 ($p = 0.75$, 95 per cent CI 0.4–3.7), and 1.0 ($p = 0.99$, 95 per cent CI 0.5–1.9), respectively.

Discussion

To our knowledge, this is the first longitudinal study of the relation between passive smoking and total and coronary heart disease mortality that has included measures of other major risk factors, objective monitoring of smoking behavior in a well defined population at risk, and a careful unbiased ascertainment and evaluation of causes of death. Our findings, which support the hypothesis that passive smoking is associated with an increase in morbidity and mortality among nonsmokers, are discussed below.

Thiocyanate levels did not vary by environmental tobacco exposure. This finding is similar to that reported by Friedman et al. (4). In other studies, conducted in smoking chambers, a direct dose-response relation between exposure to tobacco and the cotinine levels in saliva, urine, and blood was found (12). Jarvis et al. (13) also found a positive correlation between urinary cotinine levels and self-reported exposures to sidestream cigarette smoke. Similar findings using urinary cotinine were noted by Matsukura et al. (14) and Wald et al. (15). In these studies, the differences in biochemical levels by environmental exposure were small compared with the differences between smokers and nonsmokers. For example, Wald et al. reported that the median urinary cotinine levels were 1,645 ng/ml in cigarette smokers, 6 ng/ml in nonsmokers exposed to environmental tobacco smoke, and approximately 2 ng/ml in nonsmokers not so exposed.

The increase in expired air carbon monoxide resulting from passive smoking is relatively small even if statistically significant and in and of itself is of relatively little biologic significance. The increase probably reflects exposure to environmental tobacco smoke (16). The half-life of expired air carbon monoxide is somewhat short, around four hours. The men may have been exposed to their wife's tobacco smoke at home prior to going to the clinic for their annual examination or while traveling by car to the clinic. The differences in expired air carbon monoxide or blood carboxyhemoglobin levels may have been substantially greater immediately after exposure to environmental tobacco smoke. The differences presented here also may be conservative because of the fact that the smoking status of the participant's wife was available only at baseline. By the time carbon monoxide was measured, some wives who were smokers may have quit, while others who were nonsmokers may have restarted. This type of misclassification would tend to decrease any observed difference in carbon monoxide.

The health effects of exposure to low doses of carbon monoxide are not known at present. Earlier studies have reported that individuals with cardiovascular disease

(17, 18) have an adverse response to relatively low doses of environmental carbon monoxide. There has been controversy concerning these findings (19, 20), however, and the studies are currently being repeated in different laboratories. It is possible that transient elevations of carbon monoxide due to environmental tobacco smoke in high-risk individuals may be associated with an increased risk of heart attacks and perhaps cardiovascular deaths. The majority of sudden and unexpected deaths in the community occur at home (21). The acute precipitant of many of these heart attacks is unknown but could relate to certain indoor air pollutants. Occupational studies (20) of exposure to carbon monoxide and risk of heart attack have been equivocal in their results, as have community studies of the relation between ambient carbon monoxide and coronary heart disease mortality (22).

There have been a few studies of pulmonary function and exposure to passive smoking among adults (23–28). Three studies in the United States (23), France (24), and Holland (25) have demonstrated decreased pulmonary function among passively exposed individuals, with usually about a 100-ml difference in FEV_1 between the passively exposed compared with the nonexposed nonsmokers. A study in Hagerstown, Maryland (26), noted that 5 per cent of nonsmoking men not passively exposed and 7.1 per cent of those passively exposed had FEV_1 less than 80 per cent predicted (relative risk of 1.4). The relative risk was not statistically significantly different from one. Forty families were identified in a study of three communities in the United States in which the mother was a smoker and the father a nonsmoker (27). There was a statistically significant decrease in the mean residual FEV_1 for the fathers married to women who smoked compared with those married to women who did not smoke. The effect was, however, substantially reduced when the exsmoking men were excluded. A recent report from the Federal Republic of Germany (28) also failed to demonstrate any effect of passive environmental tobacco smoke on pulmonary function among a relatively young occupational cohort. There was also no apparent effect from direct cigarette smoking on either the forced vital capacity or FEV_1. Lebowitz et al. (29), in several studies in Arizona, have been unable to demonstrate any effect of environmental tobacco smoke on pulmonary function among adults who do not smoke.

The approximate 100-ml differences in the FEV_1 at baseline as noted in table 6 are consistent with those of several of the other larger studies previously discussed (23–25). It is unlikely that the relatively small differences in pulmonary function in our study can contribute substantially to chronic obstructive pulmonary disease or disability. It is possible, however, that there is a subset of individuals in whom a hypersensitivity to environmental tobacco smoke causes further progression of pulmonary disease and disability.

The excess total and coronary heart disease mortality and morbidity among MRFIT men who were exposed to environmental tobacco smoke is further evidence of a potential serious health risk for a large segment of the nonsmoking population. In the MRFIT study, 23 per cent of the men who did not smoke were exposed at home to the environmental tobacco smoke of their wives (table 1). As noted, a study by Friedman et al. (4) has suggested that up to two thirds of nonsmokers are exposed to environmental tobacco smoke. At present, the number of cancer deaths in this study is too small to allow any evaluation of the relation between environmental tobacco smoke and specific cancer and other causes of death.

Other studies have evaluated the relation between environmental tobacco smoke and lung or other cancers. Nearly all the cancer studies have been case-control studies (30–36). The cases have usually been lung or other cancers and the controls either hospital patients, community residents, or friends of the cases. Practically all the stud-

ies show a higher prevalence of exposure to passive smoking among the cases compared with the controls. The estimated odds ratios have generally ranged from 1.5 to 2.5. The largest prospective studies have been reported from Japan (37, 38) and the United States (39). In both studies, the populations at risk were predominantly women, and the exposure sources were spouses who smoked. The study in Japan by Hirayama (37, 38) demonstrated a consistent increased risk of lung cancer and other cancers among the nonsmoking wives of men who smoked. A smaller study among nonsmoking men as index subjects also demonstrated an increased risk of lung cancer among men married to women who smoked cigarettes (40).

Our findings on total and coronary heart disease mortality and morbidity are similar to those of two other studies. A study by Garland et al. (41) specifically related environmental tobacco smoke to coronary heart disease. This study followed for an average of 10 years 695 married women, initially examined in 1972–1974, in a retirement community in California. The women were classified by the self-reported smoking status of their husbands at entry into the study. After 10 years, nonsmoking wives of current or former cigarette smokers had a higher ischemic heart disease death rate than nonsmoking wives of nonsmokers. There were, however, only two ischemic heart disease deaths among the wives of the men who never smoked, 15 among the wives of former smokers, and two among the wives of current cigarette smokers. There were no differences in age-adjusted all-cause mortality rates among the wives of never, former, or current cigarette smokers. In the longitudinal study in Japan by Hirayama (40), the wives of men who smoked cigarettes also had higher coronary heart disease mortality rates.

Several reasons for the higher overall mortality among the passive smokers have been considered. First, it is possible that some passive nonsmokers were actively smoking cigarettes. The careful chemical measurements at baseline and follow-up would almost certainly rule out this hypothesis in the MRFIT study. Practically all cigarette smokers in the MRFIT study had thiocyanate levels over 100 μmol/liter. Among the passive smokers, 7.5 per cent had thiocyanate levels over 100 μmol/liter, compared with 7.3 per cent among the nonpassive smokers. If some men were smoking, they were equally divided among the two groups. A second hypothesis is that key risk factors may be different among passive and nonpassive smokers. The risk factors in the MRFIT trial, social-behavioral, physiologic, and biochemical, were generally similar between the passive and nonpassive smokers. These have been further reviewed in detail by Martin et al. (42). Adjustment for these other risk factors did not decrease the relative risks associated with passive smoking.

Third, certain other behavioral and social factors may be different among passive and nonpassive smokers. There is an inverse relation between education and other measures of social class and total coronary heart disease mortality (43). Similarly, there is an inverse relation between cigarette smoking and social class (44). Thus, it is more likely that passive smokers will be in the lower socioeconomic group. Adjustment for education or other measures of social class in the MRFIT trial did not reduce the increased relative risk. It is possible, although unlikely, that these adjustments did not completely deal with the potential differences in social and behavioral characteristics between the passive smokers and nonexposed men. More detailed analyses have failed to demonstrate other significant differences between these two groups.

Fourth, the passive smokers at baseline may have been less likely during the trial to change important risk factors that were related to subsequent mortality and morbidity. Analyses of risk factor changes in table 2 do not support this hypothesis.

Finally, follow-up was complete for all MRFIT men, and endpoints were assessed

without knowledge of passive smoking status. It is very unlikely that differential ascertainment of morbidity or mortality could account for the differences in mortality between passive and nonpassive smokers that were noted.

It is always possible that other unknown factors can explain the increased relative risk of morbidity and mortality among the passive smokers. The men were obviously not randomized to wives who smoked and to those who did not smoke. A man who did not smoke married to a woman who smoked may have had other unmeasured health behaviors that increased morbidity and mortality. The consistency of the results of the current studies with many of the other case-control and longitudinal studies plus the biologic plausibility of the hypothesis based on biochemical measurements of exposure to environmental tobacco smoke and knowledge of the pathology and physiologic changes suggest that passive smoking may result in an increased morbidity and mortality among nonsmokers.

Environmental tobacco smoke is a major indoor pollutant to which a substantial segment of the population is exposed (45). Obviously, the most successful method of reducing environmental tobacco smoke would be the further reduction of active cigarette smoking in the population. On the basis of these data, a continued reduction in active cigarette smoking will have a beneficial effect on both the cigarette smoker and on the nonsmoking population.

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